Correspondence

Penicillin allergy might not be very common in subjects with cephalosporin allergy

To the Editor:

One of the primary findings of the recent article by Romano et al[1]—that 25 of 98 patients with documented cephalosporin allergy determined by means of skin testing have clinically significant IgE-mediated allergy to penicillin—might be seriously flawed for the following reasons: The threshold used in the article for calling a penicillin skin test result positive was 3 mm, instead of the 5 mm specified in the package insert for Pre-Pen and used in the original articles on penicillin allergy skin testing.[2,3] The use of 3 mm as a positive threshold has been shown to produce much higher rates of positive penicillin skin test results in female subjects compared with use of a 5-mm threshold.[4,5] The commercial anti-penicillin IgE fluorometric enzyme immunoassays used to detect penicillin "allergy" have been shown not to correlate to penicillin skin test results and not to predict positive oral amoxicillin challenge results.[5] The high-dose amoxicillin used (20 mg/mL) for skin testing is an irritating concentration and requires a nonphysiologic pH to stay in solution. Amoxicillin has a U-shaped solubility curve, and the limit of solubility of amoxicillin in water at a pH of 7 is only 4 mg/mL.[6] The solubility of ampicillin is even lower. If these corrections are made to this article, then the rate of subjects with cephalosporin allergy who do not have a history of penicillin allergy but with true IgE-mediated allergy to penicillin might be much closer to 5%.

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Reply

To the Editor:

We read with great interest Dr Macy's observations[1] concerning our article on the cross-reactivity and tolerability of penicillins, aztreonam, and carbapenems in subjects with IgE-mediated hypersensitivity to cephalosporins[2] and specifically his claim that the results of serum specific IgE assays (ImmunoCAP; Phadia, Uppsala, Sweden), our criterion of positivity for intradermal testing, and the concentration of 20 mg/mL of ampicillin and amoxicillin in such testing led us to classify a higher number of subjects as sensitive to penicillins.

With regard to the ImmunoCAP, we totally agree that positive results on this assay do not predict a clinical reaction. In effect, we stated this in the Discussion section, in which we also reported some literature data confirming this observation.[2] In our study,[2] however, subjects with positive results to penicillin reagents did not undergo amoxicillin challenges.

As far as skin testing is concerned, we use a 3-mm wheal as the positive threshold only for skin prick tests, but as stated in the subsection on prick and intradermal skin tests,[2] we consider a positive intradermal test result when there is an *increase* larger than 3 mm in the initial wheal diameter accompanied by erythema.[3] Therefore considering that the intradermal injection of 0.02 mL of the reagent solution usually produces a wheal of 2 mm in diameter, our positive threshold is a 5-mm-diameter wheal surrounded by erythema.

For skin testing, we use amoxicillin (Amoxil; GlaxoSmithKline, Uxbridge, Middlesex, United Kingdom) and ampicillin (Amplital; Pfizer Italia, Borgo San Michele, Latina, Italy) for parenteral administration. The final concentration of these penicillins, which are sodium salts, ranges from 100 to 200 mg/mL; thus it is easy to obtain a solution of 20 mg/mL. Dr Macy instead uses the amoxicillin from Sigma (St Louis, Mo),[4] which is a trihydrate compound that, as he states, cannot be dissolved beyond 4 mg/mL unless the pH is raised to 8.5, which converts it into a sodium salt. In any case the concentration of 20 mg/mL used in amoxicillin and ampicillin intradermal testing has been widely validated.[5,6] Specifically, in a study of ours,[5] intradermal tests with amoxicillin and ampicillin proved to be nonirritating in 30 healthy control subjects who had previously been treated with 1 or more of these penicillins. Moreover, the concentration of 20 mg/mL is recommended by the European Network for Drug Allergy, the European Academy of Allergy and Clinical Immunology's interest group on drug hypersensitivity.[7] In addition, 4 of the 5 subjects with positive results on intradermal tests with either amoxicillin, ampicillin, or both at the concentration of 20 mg/mL also had positive results to at least 1 of the other penicillin reagents.

Therefore we believe that only the ImmunoCAP results concerning the 14 subjects with positive results in this test and negative results in skin tests with penicillin reagents could have entailed an overestimation of the number of subjects with cephalosporin allergy who were also sensitive to penicillins.

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